

Novartis Pharmaceuticals Corporation Comments

Draft Guidance for Industry (rev 4) - Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommended Prescribing Information for Health Care Providers and Patient Labeling

Docket No. 1998D-0834 (formerly Docket No. 98D-0834)

1. (Line 59) We recommend some sort of introductory statements that reviews the Women's Health Initiative (WHI). The results of this study have been pivotal in the creation of the black box included in this section and these same results have led to multiple revisions of the guidelines in the last few years. For example, "The Women's Health Initiative (WHI) study is the largest, randomized clinical trial to evaluate the use of hormone therapy in menopausal women. While the average age of WHI participants was 63 years, women between the ages of 50-79 were included in the trial. The prescribing information contained herein reflects the findings of the WHI as well as other past studies." A brief review of this landmark study would be useful and appropriate to include either here or in the clinical study section area.
2. (Line 66) Given the use of sonohysterography in the clinical evaluation of abnormal bleeding as well as the fact that the vaginal bleeding may be coming from a site other than the uterus, we would suggest the prescribing information not reference specific diagnostic modalities for the clinical management of undiagnosed or recurring abnormal vaginal bleeding and either provide only examples of some forms of evaluation or limit the comment to note that an adequate diagnostic evaluation be performed.
3. (Line 69) It is not clear what is meant by "natural" estrogens here.
4. (Line 87) In the final adjudicated analysis of the E+P arm, there was no statistically significant increase in the risk of myocardial infarction compared to placebo for the 5.2 years of the trial. This paragraph should clearly state that the results being reported refer to the E+P arm only.
5. (Line 96) The results of the WHIMS study are in contrast to evidence evaluating the use of hormone therapy for the slowing or prevention of cognitive decline when initiated in early menopausal or peri-menopausal women. (*References: Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology. 1992;17:485-95. Shaywitz SE, Naftolin F, Zelterman D, et al. Better oral reading and short-term memory in midlife, postmenopausal women taking estrogen. Menopause. 2003;420-26. Krug R, Molle M, Dodt C., et al. Acute influences of estrogen and testosterone on divergent and convergent thinking in postmenopausal women. Neuropsychopharmacology. 2003; 28:1538-45. Linzmayer L, Semlitsch HV, Saletu B. Double-blind, placebo-controlled psychometric studies on the effects of a combined estrogen-progestin regimen versus estrogen alone on performance, mood and personality of menopausal syndrome patients.*)

Arzneimittelforschung. 2001; 51:238-45) Since all of the participants in the WHIMS trial were over 65 years of age, the discussion in this section should note that as well as the fact that the applicability of the WHIMS results to younger women using hormone therapy is not known. The negative effect of hormone treatment on the 3MSE was noted only among women who scored below the cutoff point at baseline screening. Hormone therapy had no effect over time on women whose 3MSE scores were within the normal range at baseline. This would clearly imply that other, and perhaps more significant, factors than hormone therapy influenced the results of the WHIMS trial. While there is evidence in the literature that estrogen only therapy has no positive benefit for older postmenopausal women, and that estrogen plus progestin therapy may negatively affect the overall cognitive function of older menopausal women, the caveats of the WHIMS trial need to be noted if it serves as the chief source of factual evidence used in this guideline. It should be noted as well that the estrogen plus progestin arm of the WHIMS trial measured mean rates of change of the 3MSE while the estrogen only arm evaluated mean changes instead. (Espeland MA, Rapp SR, Shumaker SA, et al. *Conjugated Equine Estrogens and Global Cognitive Function in Postmenopausal women: Women's Health Initiative Memory Study*. *JAMA*, 2004. 291:2959-2968) Given this different measurement parameter and significant differences in the patient populations, we recommend that the guidelines clearly state that a clean, direct comparison between the results of these two studies is simply not possible.

6. (Line 102) It should be quite clear that only one formulation of estrogen and one formulation of progesterone were studied in the WHI. It is important to discriminate between forms of estrogen therapy and routes of administration as there are similar forms, e.g., percutaneous forms of estrogens, but similar forms may differ significantly in routes of administration, e.g., a gel versus a transdermal patch.
7. (Line 104) Practitioners and patients should be clear on the reasons hormone therapy is being initiated, understand the therapeutic goals, periodically re-evaluate the need for continuation of therapy, and be cognizant of both the risks and benefits of therapy for the individual patient. A recommendation for periodic re-evaluation should also be included. For these reasons, we suggest the change in wording to more accurately reflect this message, rather than a blanket statement of "lowest/shortest".
8. (Line 265) This paragraph encompasses an opportunity to raise a developmental issue. It is not completely clear if the FDA is requiring co-primary endpoints for weeks 4 and 12 or whether it is acceptable to have the primary endpoint at week 12 and a secondary endpoint at week 4.
9. (Line 265) As a developmental issue, it is important to note that these guidelines do not address the role of hormone therapy in peri-menopausal women for hot flushes yet this is a significant clinical problem. There remains no clear guidance from the FDA on what parameters would be

required to obtain approval for an indication for hormone therapy in perimenopausal women.

10. (Line 268) We would like to note the developmental issue this paragraph raises. There remains some controversy over how to measure the severity of vulvar/vaginal atrophy as well as the narrow scope of signs and symptoms currently being used in other FDA guidelines for the treatment of this condition. Perhaps this is an issue that could be addressed in future FDA discussions or requests for guideline updates.
11. (Line 279) The estrogen and combined estrogen/progesterone arms of the study required that a daily regimen was used. For completeness sake, this should be consistently stated throughout the document.
12. (Line 281) Important differences existed between the women in the E only arm in comparison to the E+P arm. This needs to be clearly stated so that readers of the package insert do not attempt to compare the results of the E only study to that of the E+P study and attribute any differences in results solely to the progesterone component.
13. (Line 285) We recommend that the statement : "The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms" be struck from the insert as there was a quality of life analysis that specifically looked at the effects of CE/MPA on hot flashes that did find a significant difference between the hormone arm and the placebo arm. (*Hays J, Ockene JK, Brunner RL, et. Al. Effects of Estrogen plus Progestin on Health-Related Quality of Life. NEJM 348(19):1839-54 at page 1840.*)
14. (Line 287) We recommend that the statement "The estrogen-alone sub-study was stopped early because an increased risk of stroke was observed" be deleted. According to the published article reporting the estrogen only arm results, the study was stopped because "(T)he NIH concluded that with an average of nearly 7 years of follow-up completed, CEE does not appear to affect the risk of heart disease, the primary outcome of the study." The same article also noted that none of the predefined stopping boundaries had been crossed, although the stroke comparison was *approaching* the adverse effect boundary. It would seem that the study was stopped primarily because neither cardioprotection nor breast cancer risk would be demonstrated in the remaining intervention period, not because there was an increase in stroke that exceeded either the predefined stopping boundary or the risk demonstrated in the estrogen plus progestin trial.
15. (Line 291, 311) We would recommend that the demographics of each arm of the WHI be included in the introduction of the guidelines or immediately prefacing the black box. An alternative to this recommendation would be to include an introductory review, including demographics, of the estrogen only arm that is separate from an introductory review which includes demographics of the estrogen plus progestin arm at the beginning of the draft guidance. We believe this is important because the original study plan was to have 20% of overall minority ethnic group enrollment but only 16.03% of the enrollment target was achieved. (*The Women's Health Initiative Study Group. Design of Women's Health Initiative clinical trial and*

observational study. Control Clin Trials. 1998;19:61-109.) In general, the power of the WHI was not sufficient to represent ethnic groups as a whole or any single, specific ethnic group. The power of the WHI was adequate for Caucasian women but the number of non-Caucasian participants was not sufficient to allow for clear application of the results to minority groups. In addition, the demographics cited here included only three ethnic groups. We recommend that the summary statistic of the other groups included in the study also be noted for completeness sake.

16. (Line 298, 320) For the most accurate description of the WHI, we strongly urge the inclusion of both the nominal and adjusted relative risks and confidence intervals in all tables in the document. In some categories, the nominal confidence interval and hazard ratio has shown significance while the adjusted confidence interval and hazard ratio in the same category does not. This remains a controversial point of the WHI study and as such, both sets of data should be presented in an effort to be as thorough and complete as possible.
17. (Line 326) The guidance document does not consistently put quotation marks around the words global index.
18. (Line 333) The population of women in the estrogen only arm had a higher incidence of obesity, diabetes, history of stroke, and hypertension than the population in the estrogen plus progestin arm. In the WHI overall, 69.25% of participants were overweight and obese, approximately 36% of women were hypertensive, and 18% were being treated for hypercholesterolemia. In fact, in the interventional group, a total of 6645 (78%) women were sick or had a history of illnesses. Therefore, 78% of the subjects in the WHI trial overall did not qualify as a healthy population. It is quite arguable therefore, that they were not 'predominantly healthy'.
19. (Line 347) We would recommend that where possible a "%" sign be used in lieu of writing out the word percent.
20. (Line 371) We recommend that the term local be used in lieu of topical as there are estrogen modalities, e.g., Estring, that are local estrogen agents and are not topical. If it is necessary to include the use the word topical, we would ask that the word local also be included in the sentence.
21. (Line 405) Neither the estrogen alone or estrogen plus progestin arms of the WHI demonstrated a statistically significant increase in the risk of myocardial infarction; this should be clearly and consistently reflected in the guidance.
22. (Line 421) In the final analysis, there was not a significant difference between the active treatment arms and the placebo arms- the guidance needs to reflect this.
23. (Line 423) While there was a significant difference in CHD events between the two groups during year one, there was not a significant difference thereafter.
24. (Line 470) We recommend adding the phrase as shown for further clarity of the statement. Concomitant use of estrogen with progestin (in proper doses and duration) in women with an intact uterus is not associated with an

- increase in the risk of endometrial cancer. As written, the statement implies that use of estrogen at all in women with an intact uterus, with or without proper doses of progestin, will lead to an increased risk of endometrial cancer.
25. (Line 474) We recommend the inclusion of the additional words for further clarity.
 26. (Line 479) We recommend this additional wording for completeness sake.
 27. (Line 488) We find the paragraphs in this section to be unclear.
Observational trials should not be used to corroborate the findings of randomized trials in an evidence-based document. This is particularly true when the observational trials performed over time have not been overwhelmingly consistent. Some observational trials have shown an increase in breast cancer risk, others have shown a decrease, and others have shown no difference between treatment and placebo groups.
 28. (Line 493) See comment 27.
 29. (Line 494) See comment 27. If this statement is to be retained for use, it is important to note that this statement implies a definitive linear increase in risk with increasing duration of use. This has not been seen in all studies. For example, in the Nurse's Health Study and in the Collaborative Group Study, there was no significant increase in breast cancer among women using it for 10-14 years, although it was significant for years 5-10 and years 15+.
 30. (Line 496) See comment 27. If this sentence is to be retained however, we recommend wording the sentence as we have done for improved precision.
 31. (Line 499) See comment 27. As originally written, the sentence makes it sound as if this is a definitive fact and it simply is not.
 32. (Line 506, 509) We recommend that for consistency's sake, the 95% CI be included whenever a hazards ratio, absolute risk, or relative risk is cited.
 33. (Line 511) See comment 27. If this sentence is retained as it is, we note that this has not been seen in other (observational) studies; as previous paragraphs on this topic mention the results of observational studies, they should be mentioned here as well.
 34. (Line 571) A comment on the decrease in endometrial cancer associated with combination therapy should be included here as well.
 35. (Line 576) We believe this wording is more accurate.
 36. (Line 618) This sentence is vague in connoting the statistical significance of this finding but is more accurately reflected or noted in the sentence that follows that includes the CI. We recommend this sentence be deleted.
 37. (Line 646) We believe this word changing more accurately reflects clinical practice.
 38. (Line 657) All of the increased test results should be listed together followed by all of the decreased results for easier reading and clarity.
 39. (Line 680) Proper doses and duration of progestin use with estrogens does not increase the risk of endometrial cancer.

40. (Line 680) The increase in invasive cancer was seen only in the estrogen plus progestin arm of the WHI; it was not seen in the estrogen only arm. The wording of this paragraph should reflect this.
41. (Line 681) The WHI did not demonstrate a significant increase in the risk of ovarian cancer with hormone therapy. This should not be included as a risk.
42. (Line 684) It is not clear what is meant by 'natural' estrogen here.
43. (Line 710) We recommend the change in wording for clarity and ask that the confidence intervals be cited here to allow the reader to determine if the difference in the risk of stroke between the two groups was statistically significant.
44. (Line 715) For clarity, a comment noting there was no significant difference in probable dementia between placebo and estrogen should be included here.
45. (Line 720) The confidence intervals should be included here to allow the prescriber to determine if this difference between groups was statistically significant.
46. (Line 757) We recommend the word change for improved clarity.
47. (Line 759) We recommend the word change for improved clarity.
48. (Line 795) As a development recommendation, we ask the FDA to consider how to address the mood changes or changes in sleep patterns in this section.
49. (Line 812) See comment 6.
50. (Line 821) As a future development issue, vaginal treatment is often tailored (in terms of frequency and dosing) to meet individual needs but there is little in this or other guidelines that allow for or discuss the individualization of therapy for topical or intravaginal treatments for VVA.
51. (Line 860) Unopposed estrogens in the presence of an intact uterus increase the risk of endometrial cancer. The use of estrogen and progestin (in proper doses and for proper durations) does not increase the risk of uterine cancer. We recommend wording this statement to more accurately reflect this.
52. (Line 870) In the final adjudicated analysis of the E+P arm, there was no statistically significant increase in the risk of myocardial infarction compared to placebo for the 5.2 years of the trial. In the E only trial results to date, there is no statistically significant increase in the risk of myocardial infarction compared to placebo. We would recommend that the statement be modified such that the category of heart disease not be mentioned in this sentence
53. (Line 874) Only the estrogen plus progestin arm of the WHI showed an increase risk in probable dementia. This statement is inaccurate as it is currently written.
54. (Line 905, 909) Some women report irritation around the vagina but not within it in the presence of vulvovaginal atrophy.
55. (Line 947) We recommend the word change for improved clarity.
56. (Line 977) We recommend the word change for improved clarity.

57. (Line 988) See comment 53. This section refers to the possible side effects of estrogens and does not explicitly state or imply the use of progestins.
58. (Line 990) See comment 49.
59. (Line 1015) This is not a common side effect of estrogen therapy.